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Cerebrovascular disease in COVID-19: a systematic review and meta-analysis

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SUMMARY

Background: The association between COVID-19 and acute cerebrovascular disease (CVD) has not been explored extensively. New data has come to light which may change previous results.
Methods: We queried the PubMed electronic database from its inception until February 2022 for studies evaluating the incidence of stroke in COVID-19 patients. Results of the analysis were pooled using a random-effects model and presented as odds ratios (ORs) with 95% confidence intervals (95% CIs).
Results: 37 studies consisting of 294,249 patients were included in our analysis. Pooled results show that the incidence of acute CVD events in COVID-19 positive patients is 2.6% (95% CI: 2.0-3.3; P<0.001). Cardioembolic (OR=14.15, 95% CI: 11.01 to 18.19, P<0.00001) and cryptogenic (OR=2.87, 95% CI: 1.91 to 4.32, P<0.00001) etiologies were associated with COVID-19 positivity. Risk factors for CVD events in patients with COVID-19 were atrial fibrillation (OR=2.60, 95% CI: 1.15 to 5.87, P=0.02), coronary artery disease (OR=2.24, 95% CI: 1.38 to 3.61, P=0.0010), diabetes (OR=2.46, 95% CI: 1.36 to 4.44, P=0.003) and hypertension (OR=3.65, 95% CI: 1.69 to 7.90, P=0.005).
Conclusion: COVID-19 infection is associated with an increased risk for acute CVD and is associated with cardioembolic and cryptogenic etiologies and the risk factors of atrial fibrillation, coronary artery disease, diabetes and hypertension in COVID-19 positive patients.

Keywords: Stroke, COVID-19, SARS-CoV-2, acute cerebrovascular disease, CVD.

INTRODUCTION

COVID-19, also known as SARS-CoV-2, is a single-stranded positive-sense RNA virus that was discovered in the Chinese province of Wuhan. It has since spread throughout the world to pandemic levels due to its extremely high infection rate, incubation period, and proclivity for recombination and rapid mutation [1-4].
While the SARS coronavirus (CoV) primarily affects the respiratory system, it is also known to increase the risk of cardiovascular disease and has also been shown to increase the risk of acute cerebrovascular disease (CVD). Multiple of studies on the effects of this novel coronavirus infection of the brain have been completed, with Nannoni et al. publishing a meta-analysis in 2021 highlighting the association between COVID-19 incidence and CVD [5, 6]. Given that new data to this end has emerged over time, we felt it was necessary to up-

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date this study. This is particularly true considering that a number of recent high-powered studies, including those conducted by Ramos-Araque et al., and Katsoularis et al. found that COVID-19 positivity was not a significant risk factor for CVD incidence, a finding that contradicts Nannoni et al. [6-8]. As a result, we believed that these new studies could significantly alter the previous findings. This is substantial because, in the midst of a global pandemic, it is critical to identify groups at higher risk of infection-related complications and modify treatment and prophylaxis guidelines accordingly. The purpose of this study is to investigate the incidence of CVD in Covid-19 positive patients, as well as the risk factors and specific aetiology and characteristics of Covid-associated stroke, as well as to compare the likelihood of developing acute CVD events in patients positive and negative for COVID-19 infection.

METHODOLOGY

Data sources and search strategy

This systematic review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [9]. Based on MEDLINE and Embase databases with no language restrictions, an extensive electronic literature search was collected from December 2019 - February 2022 by two researchers (AKS and MTM) independently, for all relevant studies having acute cerebrovascular disease (CVD) incidences in COVID-19 patients. For purpose to making sure that all important publications were included, the snowballing approach was used and hand searches of all reference lists of eligible articles were conducted. Duplications were identified and removed from all retrieved articles using Endnote X7 (Clarivate Analytics, PA). To avoid overlapping, the meta-analysis of the respective outcome only included the latest study from the studies reported by the same author or institution and conducted in the same period with the same outcomes. The search string used was: (((Covid-19) OR (Covid19) OR (2019-nCoV) OR (SARS CoV-2) OR (SARS-CoV-2) OR (SARS-CoV) OR (2019 novel coronavirus)) AND ((Stroke) OR (Acute cerebrovascular disease) OR (cerebral thrombosis) OR (brain infarction) OR (intracranial hemorrhage) OR (ischemic stroke) OR (hemorrhagic stroke))).

Study selection

This meta-analysis is included and merged retrospective cohort studies, case-control studies, and case-series accounting incidence of acute cerebrovascular disease (CVD) events in patients with COVID-19 infection, risk factors of stroke incidence in COVID-19 patients, and stroke etiology in stroke patients with and without COVID-19. Inclusion criteria contained the studies included at least five cases of COVID-19 patients developing acute CVD. All animal studies, case reports, editorials, studies having less than five cases, and studies without full-text available were excluded.

Data Extraction and Quality Assessment

Based on the titles and abstracts, two researchers (AKS and MTM) filtered studies based on titles and abstracts, depending on the inclusion criteria. Studies that met the inclusion criteria were reviewed and analyzed thoroughly. The data was extracted and cross-checked by the two researchers and for each study, the following set of data was extracted: General information (the first author's last name, publication year, study setting, sample size, participant's sex and age), study design, outcomes and aims of meta analysis. Lastly, publication bias was assessed by using funnel plots statistically and visually, where it was considered significant if the p-value was less than 0.05. To evaluate the quality of included studies, The Newcastle-Ottawa scale (NOS) was used [10]. Two researchers (AMAD and MWAA) performed the quality assessment for included studies. In cases of disagreement, a third researcher (HWA), was consulted for a final decision.

Statistical Analysis

Review manager, version 5.4 (Nordic Cochrane Center Copenhagen, Denmark) and OpenMeta-Analyst was used for statistical analysis [11]. Frequencies of patients with the Incident of acute CVD among COVID-19 patients were calculated and was presented as a proportion by dividing the patient with acute CVD by the total number of COVID-19 patients. Odds ratio (OR) estimates with 95% confidence intervals (CIs) was used to represent other dichotomous outcomes i.e risk factors for stroke incidence in COVID-19 patients with and without acute CVD and stroke etiologies among COVID-19 patients with stroke and non-COVID-19 patients with stroke. The results were

pooled using random effects model [12]. Forest plots were created to visually assess the result of pooling. The Higgins I^2 statistic was analyzed to assess heterogeneity and a value of less than 50% was acceptable. A visual inspection of Funnel Plot was conducted to evaluate potential publication bias. A p-value of less than 0.05 was considered significant in all cases.

RESULTS

Study selection, trial characteristics and quality assessment

Initial search of PubMed/Medline database yielded a total of 5,877 unique hits. The first round of screening using title and abstract resulted in the identification of 74 relevant studies. After the duplicates were removed, further assessment of the full-text lead to the inclusion of 37 unique relevant studies in our meta-analysis [13-49]. Studies with at least five patients reporting the incidence of acute CVD in COVID-19 patients with relevant outcomes were included in our analysis. The PRISMA flowchart summarizing the study selection process is provided in Figure 1. The total number of patients included in our analysis were 294,249. The studies comprised of case-series, case-control and retrospective cohort studies. The baseline study characteristics are summarized in Table 1. The results of quality assessment are provided in Supplementary Table S1. All studies were of reasonably high methodological quality. Symmetry in the funnel plot (Figure S1) suggests no small study or publication bias.

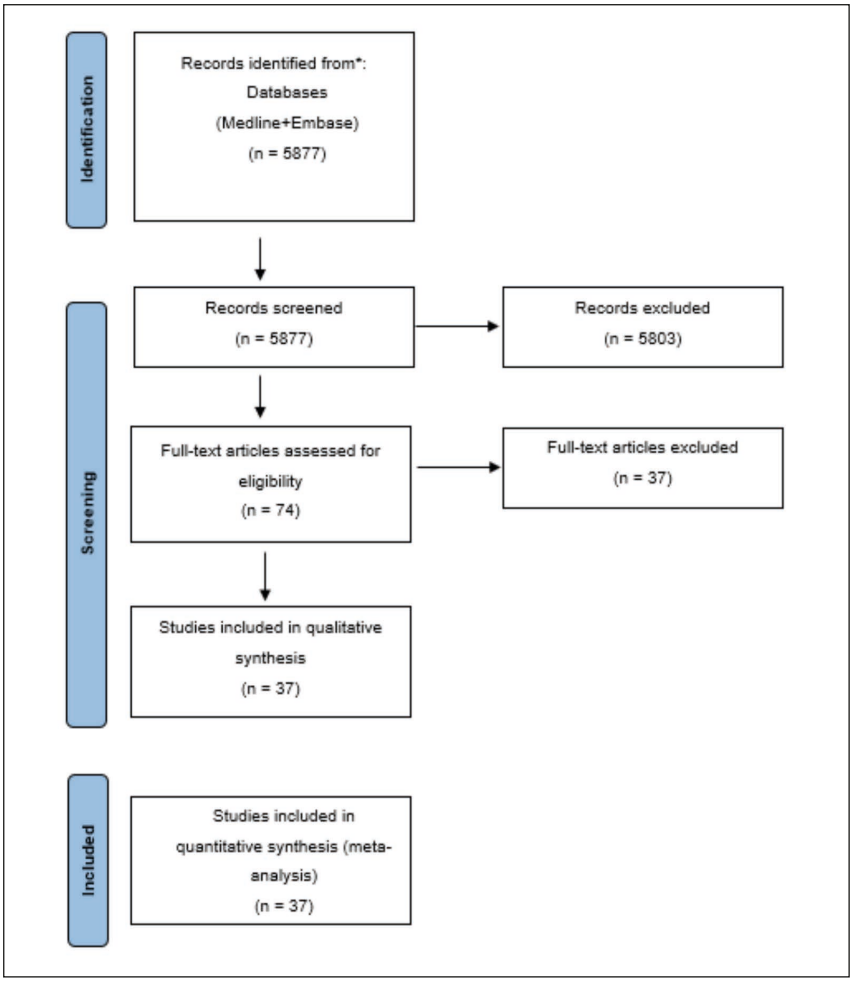

Figure 1 - PRISMA flowchart summarizing results of the literature search.

Table 1 - Baseline characteristics of the included studies.

Study	*Country*	*Study design*	*Covid-19 patients*	*Covid-19 patients with acute CVD*	*Mean age (years)*	*Reported outcomes*
1. Altschul DJ et al. [13]	USA	Retrospective observational	5227	35	67	Stroke incidence, stroke characteristics
2. Annie F et al. [14]	USA	Retrospective observational	9358	64	-	Stroke incidence, risk factors for stroke, stroke characteristics
3. Dogra S et al. [15]	USA	Retrospective observational	3824	33	62	Stroke incidence, stroke characteristics
4. Jain R et al. [16]	USA	Retrospective observational	3218	35	66	Stroke incidence, stroke characteristics
5. Katz JM et al. [17]	USA	Retrospective observational	10596	86	38	Stroke incidence, stroke characteristics, clinical outcomes of Covid-19 associated stroke
6. Kvernland A et al. [18]	USA	Retrospective observational	4071	19	60	Stroke incidence, stroke features, clinical outcomes of Covid-19 associated stroke
7. Merkler AE et al. [49]	USA	Retrospective observational	2132	31	69	Stroke incidence, risk factors for stroke, stroke features
8. Nalleballe K et al. [20]	USA	Retrospective observational	40469	406	–	Stroke incidence
9. Pinna P et al. [21]	USA	Retrospective observational	650	19	–	Stroke incidence, stroke features
10. Rothstein A et al. [22]	USA	Retrospective observational	844	28	60.5	Stroke incidence, stroke features
11. Siegler JE et al. [23]	USA	Retrospective observational	14483	172	–	Stroke incidence, stroke features
12. Yaghi S et al. [24]	USA	Retrospective observational	3556	32	63	Stroke incidence, stroke features
13. Cantador E et al. [25]	Spain	Case series	2115	8	76.4	Stroke incidence, stroke features
14. Chougar L et al. [26]	France	Retrospective observational	1176	18	–	Stroke incidence
15. Hernandez-Fernandez F et al. [27]	Spain	Retrospective observational	1683	23	–	Stroke incidence, stroke features, clinical outcomes of Covid-19 associated stroke
16. Klok FA et al. [28]	Netherlands	Retrospective observational	184	5	–	Stroke incidence, stroke features
17. Lodigiani C et al. [29]	Italy	Retrospective observational	388	9	71	Stroke incidence, stroke features
18. Pons-Escoda A et al. [30]	Spain	Retrospective observational	2249	20	71	Stroke incidence, stroke features
19.Fan S et al. [31]	China	Retrospective observational	86	6	68.2	Stroke incidence, stroke features, risk factors for stroke
20. John S et al. [32]	UAE	Retrospective observational	673	20	46.5	Stroke incidence, stroke features
21. Karadas O et al. [33]	Turkey	Retrospective observational	239	9	–	Stroke incidence

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Study	Country	Study design	Covid-19 patients	Covid-19 patients with acute CVD	Mean age (years)	Reported outcomes
22. Li Y et al. [34]	China	Retrospective observational	221	13	73.5	Stroke incidence, stroke features, risk factors for stroke
23. Mao L et al. [35]	China	Retrospective observational	214	6	–	Stroke incidence, stroke features
24. Xiong W et al. [36]	China	Retrospective observational	917	10	–	Stroke incidence, stroke features
25. Dhamoon et al. [37]	USA	Retrospective observational	277	105	66.7	Stroke incidence
26. Ming Tu et al. [38]	Singapore	Case series	18	18	41	Stroke incidence
27. Rass et al. [39]	Austria	Prospective observational	135	1	–	Stroke incidence
28. Katsoularis et al. [40]	Sweden	Case series	83486	30	–	Stroke incidence
29. Qureshi et al. [41]	–	Retrospective observational	8163	103	54.4	Stroke incidence, risk factors for stroke incidence
30. Pezzini et al. [42]	Italy	Prospective observational	1013	160	75.5	Stroke incidence
31. Nersesjan et al. [43]	Denmark	Prospective observational	61	4	–	Stroke incidence
32. Calmettes et al. [44]	France	Retrospective observational	216	40	68	Stroke incidence
33. Jillela et al. [45]	USA	Case series	396	13	61.6	Stroke incidence
34. Sluis M et al. [46]	–	Prospective observational	2147	38	74.5	Stroke incidence, risk factors for stroke
35. Ramos-Araque et al. [47]	–	Case series	14483	156	–	Stroke incidence, stroke features
36. Khedr et al. [48]	Egypt	Retrospective observational	439	42	–	Stroke incidence, risk factors for stroke
37. Garcia-Lamberechts et al. [49]	Spain	Retrospective observational	74814	147	76	Stoke incidence, stroke features, risk factors for stroke incidence

Results of meta-analysis

Detailed forest plots showing results of this meta-analysis are provided in the online supplementary data (supporting information Figure S2 - S12; online supplementary data).

Incidence of acute CVD in COVID-19 patients (single arm analysis): Out of the 37 selected studies, all the studies reported incidence of acute CVD in COVID-19 patients (total, 294,249; events, 1963). Our pooled analysis demonstrates that the incidence of acute CVD in COVID-19 patients is 2.6% (95% CI: 2.0-3.3; P<0.001; Figure 2).

Incidence of acute CVD in COVID-19 patients (double arm analysis): 3 selected studies reported incidence of acute CVD in COVID-19 patients (total cases, 166,493; events, 280) with a dual-arm analysis (total controls, 1,749,344; events, 6,772). Our pooled analysis demonstrates that the incidence of acute CVD in COVID-19 vs non-COVID-19 patients is 1.16 (95% CI: 0.43-3.14; P=0.77; Figure 3).

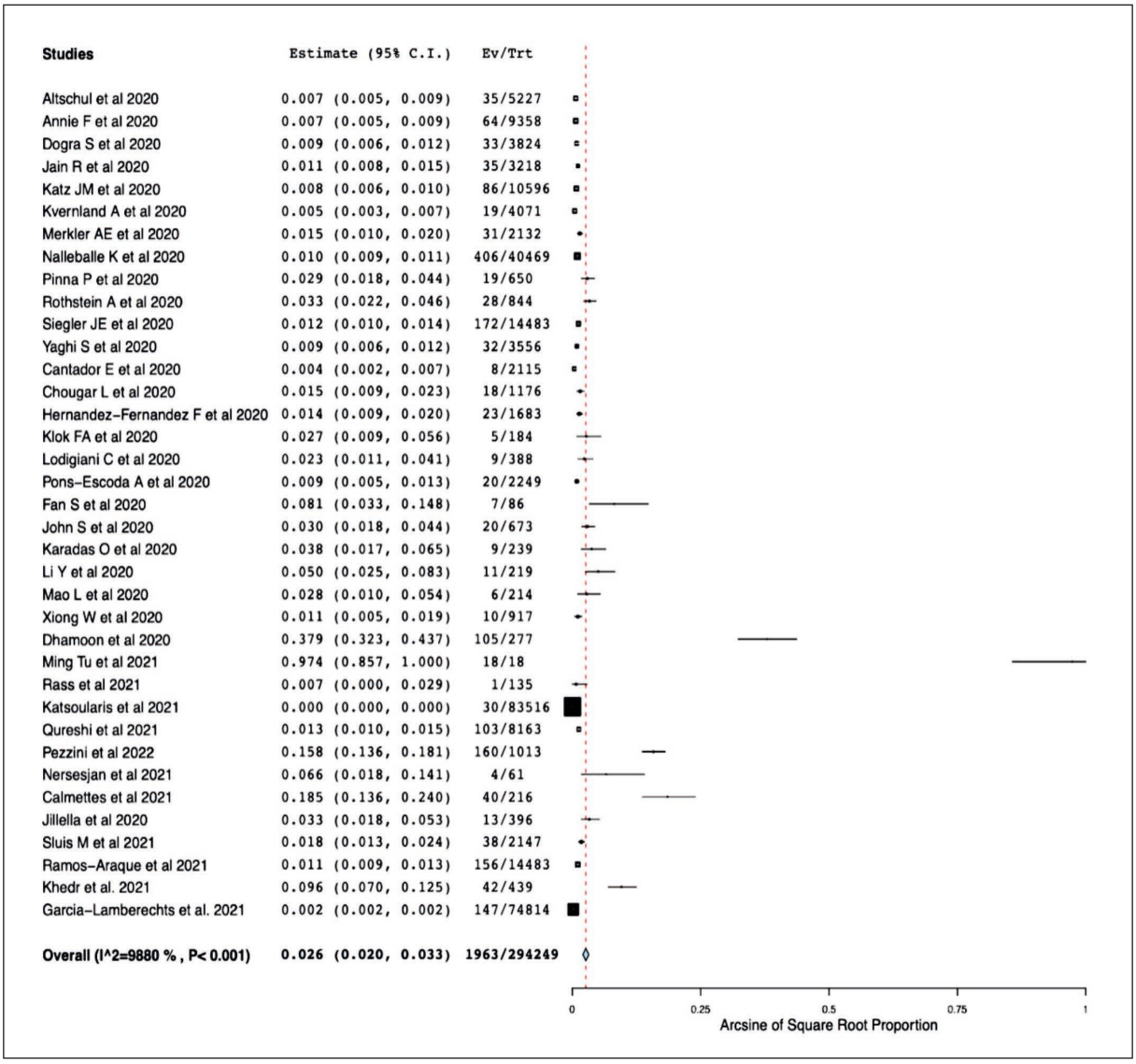

Figure 2 - Forest plot of single-arm analysis of CVD incidence in COVID-19 patients.

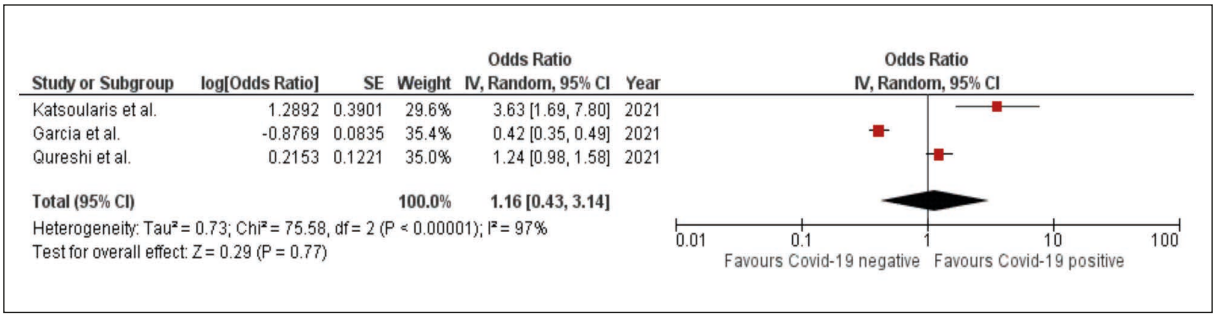

Figure 3 - Forest plot of dual-arm analysis of CVD incidence.

Risk factors for stroke incidence in COVID-19 patients: seven studies were available to compare clinical characteristics of COVID-19 patients with CVD (n= 456) and without CVD (n= 22076), (Figure 4).
Diabetes: Out of the 7 studies, all the studies reported for diabetes in COVID-19 patients with CVD (total, 309; events, 135) and without CVD (total, 21782; events, 4474). Our pooled analysis demonstrates that COVID-19 patients with CVD were significantly associated with greater likelihood of having diabetes than COVID-19 patients without CVD (OR=2.46, 95% CI: 1.36 to 4.44, P=0.003; Figure S4).
Hypertension: Out of the 7 studies, all the studies reported for hypertension in COVID-19 patients with CVD (total, 309; events, 214) and without CVD (total, 21782; events, 7214). Our pooled analysis demonstrates that COVID-19 patients with CVD were significantly associated with greater likelihood of having hypertension than COVID-19 patients without CVD (OR = 3.65, 95% CI: 1.69 to 7.90, P=0.005; Figure S5).
Coronary artery disease: Out of the 7 studies, 5 studies reported for coronary artery disease in COVID-19 patients with CVD (total, 234; events, 48) and without CVD (total, 12280; events, 1340). Our pooled analysis demonstrates that COVID-19 patients with CVD were significantly associated with greater likelihood of having coronary artery disease than COVID-19 patients without CVD (OR=2.24, 95% CI: 1.38 to 3.61, P=0.0010; Figure S6).
Atrial fibrillation: Out of the 7 studies, 5 studies reported atrial fibrillation in COVID-19 patients with CVD (total, 233; events, 52) and without CVD (total, 12064; events, 1356). Our pooled analysis demonstrates that COVID-19 patients with CVD were significantly associated with greater likelihood of having atrial fibrillation than COVID-19 patients without CVD (OR = 2.60, 95% CI: 1.15 to 5.87, P=0.02; Figure S7).
Female sex: Out of the 7 studies, all the studies reported female sex in COVID-19 patients with CVD (total, 309; events, 157) and without CVD (total, 21782; events, 11686). Our pooled analysis demonstrates no significant relation with regards to sex difference (OR=1.01, 95% CI: 0.80 to 1.27, P=0.93; Figure S8).
Kidney injury (acute/chronic): Out of the 7 studies, 6 studies reported kidney injury in COVID-19 patients with CVD (total, 297; events, 76) and without CVD (total, 21358; events, 3811). Our pooled analysis demonstrates no significant relation with kidney injury and the risk of stroke in COVID-19 patients (OR=1.48, 95% CI: 0.70 to 3.15, P=0.35; Figure S9).
Chronic obstructive pulmonary disease (COPD): Out of the 7 studies, 4 studies reported COPD in COVID-19 patients with CVD (total, 188; events, 12) and without CVD (total, 13672; events, 1905). Our pooled analysis demonstrates no significant relation with COPD and the risk of stroke in COVID-19 patients (OR=0.71, 95% CI: 0.31 to 1.67, P=0.40; Figure S10).
Smoking: Out of the 7 studies, 3 studies reported smoking in COVID-19 patients with CVD (total, 174; events, 34) and without CVD (total, 16980; events, 1210). Our pooled analysis demonstrates no significant relation with smoking and the risk of stroke in COVID-19 patients (OR=2.14, 95% CI: 0.63 to 7.26, P=0.28; Figure S11).

Stroke etiologies among stroke patients with and without COVID-19
Total stroke patients with COVID-19 were (n=1294), and total stroke patients without COVID-19 (n=17393), (Figure 5).

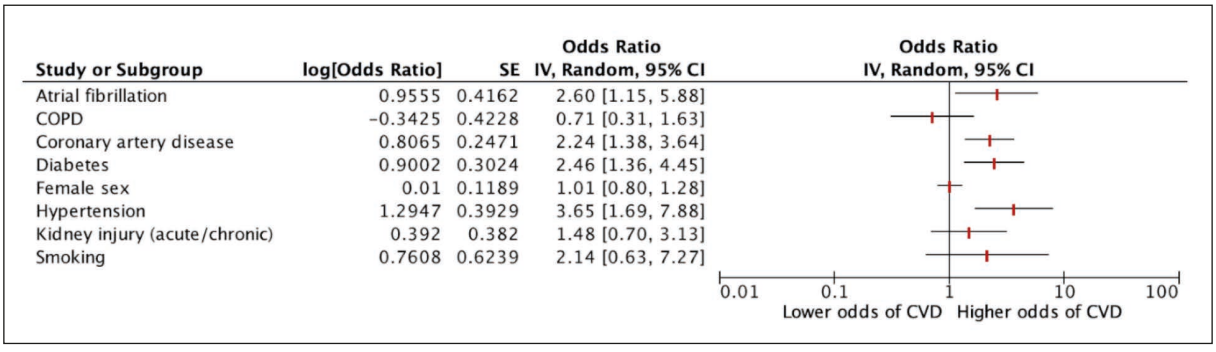

Figure 4 - Summary plot of risk factors for stroke incidence in COVID-19 patients.

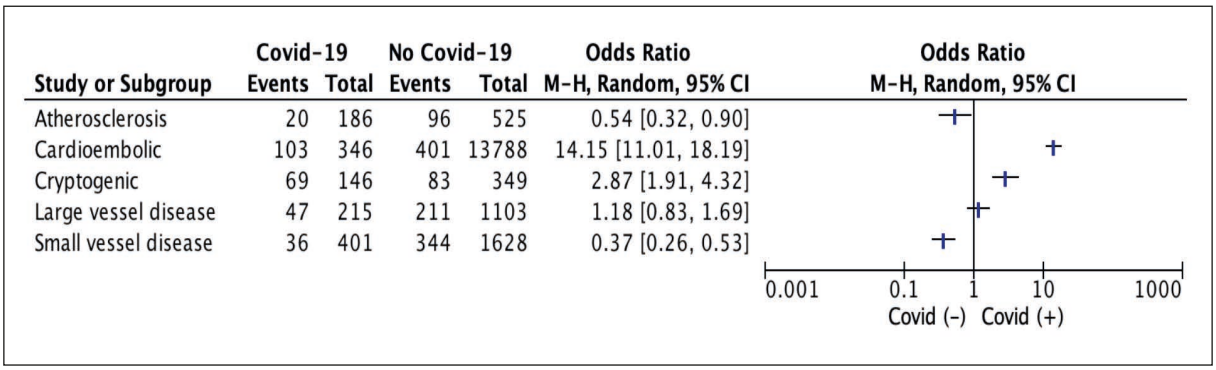

Figure 5 - Forest plot of stroke etiologies among stroke patients with and without COVID-19.

Atherosclerosis: Atherosclerosis in stroke patients with COVID-19 was (total, 186; events, 20) and in stroke patients without COVID-19 (total, 525; events, 96). Our pooled analysis demonstrates significantly higher odds of atherosclerotic events in stroke patients without COVID-19 (OR=0.54, 95% CI: 0.32 to 0.90, P=0.02).

Cardioembolic: Cardioembolism in stroke patients with COVID-19 was (total, 346; events, 103) and in stroke patients without COVID-19 (total, 13788; events, 401). Our pooled analysis demonstrates significantly higher odds of cardioembolic events in stroke patients with COVID-19 (OR=14.15, 95% CI: 11.01 to 18.19, P<0.00001).

Cryptogenic: Cryptogenic type in stroke patients with COVID-19 was (total, 146; events, 69) and in stroke patients without COVID-19 (total, 349; events, 83). Our pooled analysis demonstrates significantly higher odds of cryptogenic events in stroke patients with COVID-19 (OR=2.87, 95% CI: 1.91 to 4.32, P<0.00001).

Large vessel disease: Large vessel disease in stroke patients with COVID-19 was (total, 215; events, 47) and in stroke patients without COVID-19 (total, 1103; events, 211). Our pooled analysis demonstrates that the incidence of large vessel disease in stroke patients with and without COVID-19 was non-significant (OR=1.18, 95% CI: 0.83 to 1.69, P=0.36).

Small vessel disease: Small vessel disease in stroke patients with COVID-19 was (total, 401; events, 36) and in stroke patients without COVID-19 (total, 1628; events, 344). Our pooled analysis demonstrates significantly higher odds of small vessel disease events in stroke patients without COVID-19 (OR=0.37, 95% CI: 0.26 to 0.53, P<0.00001).

DISCUSSION

In this study, we analyze 37 studies which included 230,031 patients, and our results showed that there is a significant association between acute cerebrovascular disease (CVD) and Covid-19. We found that Covid-19 positive patients are at higher risk to develop CVD than negative patients. The incidence is 2.7% (95% CI: 2.1-3.5, P<0.001). The etiologies were associated with CVD in COVID-19 positive patients are cardioembolic and cryptogenic. While other etiologies such as atherosclerosis and small or large vessel diseases were not associated with COVID-19 positivity. The common risk factors found in COVID-19 positive patients that increase the likelihood of CVD were atrial fibrillation, coronary artery disease, diabetes, and hypertension. Although there is a relation between COVID-19 and CVD, it might be only a correlation not a causation. This is because that the studies, which were included, evaluate the outcomes that are only found in hospitalized COVID-19 patients, without including other milder cases or even asymptomatic patients outside the hospital.

As our novel finding indicates that COVID-19 positivity is significantly associated with CVD, there might be a biological plausibility of Coronavirus itself being an independent risk factor. Due to the fact that atherosclerosis and small vessel disease were not found as etiologies in COVID-19 patients with CVD, Coronavirus may have an underlying pathophysiology. The hypercoagulable state in the disease manifestation, which is presented as high levels of D-dimer, fibrinogen, factor VIII (FVIII), von Willebrand factor (vWF), and decreased antithrombin as well as low TEG test re-

sults [50-54]. Also, COVID-19 positive patients, as one study demonstrated, lack a clot lysis [55], with another study found that patients with Covid-associated pneumonia had higher levels of platelets than seen in cases of severe pneumonia [56]. Although the underlying pathophysiology is poorly understood currently, the results of Covid infection being a risk of thromboembolic events are consistent with our finding, that is, COVID-19 positive patients have higher risk for cardioembolic and cryptogenic stroke, with lower risk of developing CVD as a result of atherosclerosis and both large and small vessel disease.

One important finding in our study is the incidence of CVD that was higher than what was expected. The global pandemic is affecting millions and the difference may be limited to only 1-2% but at the same time the implications of the potential stroke complications alone would be assessed in the tens of thousands, internationally. Our findings also refined those who were previously infected with COVID-19 – associated CVD to evaluate other risk factors and to focus on individuals who are more prone to have complications. Our findings aimed to find Covid 19 as an independent risk factor for stoke in our analysis. Nannoni et al. [6] have worked previously on this concept although due to other risk factors and comorbidities, this might have been a product of confounding bias. Due to this, there are conflicts related to COVID-19 being causally associated with stroke.

Consequently, a greater attention should be shifted toward positively infected COVID-19 patients due to the fact of being at a high risk of developing CVD, specifically in healthcare sittings. In addition to the importance of observing any new development of neurological clinical features that should be immediately evaluated to prevent CVD events or further complications.

COVID-19 should be considered in patient who presents with acute CVD events until Covid 19- is being excluded from diagnosis. Till then all measures of precautions should be taken into consideration to reduce COVID-19 spread and the impact of CVD.

In our study, one main limitation was the high grade of results heterogeneity in most analysis. This is due to the use of different study designs between the studies in our analysis. The increase of heterogeneity is resulted from the variation of Sample sizes, study protocols and specific choice of controls, historical or current. In addition, since COVID-19 pandemic is still a recent phenomenon these findings may still be considered preliminary. The pathophysiology and effect of COVID-19 on the brain is still needing further study because the current knowledge regarding this topic isn't enough to estimate an underlying causational basis for our results. We encourage conducting Future studies that comprehend the underlying mechanisms that makes COVID-19 infection associated with a high risk of developing CVD. More data is needed to know if our findings were correlational or whether it is a result of a causative relationship and to have more precise effect sizes for both the incidence of CVD in Covid patients and the resulted CVD risk from COVID-19 positivity.

CONCLUSION

COVID-19 infection is independently associated with high risk of developing stroke and presents with a higher incidence than demonstrated previously. Stroke is associated with cardioembolic and cryptogenic aetiologies and the risk factors of atrial fibrillation, coronary artery disease, diabetes, and hypertension in COVID-19 positive patients.

Funding
None

Conflicts of interest
None

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Table S1 - Quality assessment of the observational studies included in the meta-analysis based on the Newcastle-Ottawa scale.

Paper	*Selection*				*Comparability*		
First author	*Representativeness of the exposed cohort*	*Selection of the non exposed cohort*	*Ascertainment of exposure*	*Demonstration that outcome of interest was not present at start of study*	*Comparability of cohorts on the basis of the design or analysis*	*Assessment of outcome*	*Ou*
Altschul DJ et al.	*	*	*	*	**	*	
Annie F et al.	*	*	*	*	**	*	
Dogra S et al.	*	*	*	*		*	
Fan S et al.	*	*	*	*	**	*	
HernándezFernández F et al.	*	*	*	*	**	*	
Jain R et al.	*	*	*	*		*	
John S et al.	*		*	*		*	
Karadas O et al.	*	*	*	*		*	
Katz JM et al.	*	*	*	*	**	*	
Klok FA et al.	*	*	*	*		*	
Kvernland A et al.	*	*	*	*	**	*	
Li Y et al.	*	*	*	*	**	*	
Lodigiani C et al.	*	*	*	*		*	
Mao L et al.	*	*	*	*		*	
Merkler AE et al.	*	*	*	*	**	*	
Nalleballe K et al.	*	*	*	*		*	
Pinna P et al.	*	*	*	*		*	
Pons-Escoda A et al.	*	*	*	*		*	
Rothstein A et al.	*	*	*	*		*	
Siegler JE et al	*		*	*		*	
Xiong W et al.	*	*	*	*		*	
Yaghi S et al.	*	*	*	*	**	*	
Cantador E et al.	*	*	*	*	**	*	
Chougar L et al.	*	*	*	*		*	
Dhamoon et al.	*	*	*			*	
Rass et al.	*	*	*	**	*	*	
Katsoularis et al.	*	*	*	*			
Qureshi et al.	*	*	*	*		*	
Pezzini et al.	*	*	*	*	*	*	
Nersesjan et al.	*	*	*	*	*	*	
Calmettes et al.	*	*	*	*		*	
Jillela et al.	*	*	*	**	*		
Sluis M et al.	*	*	*	*	**	*	
Ramos-Araque et al.	*	*	**		*	*	
Khedr et al.	*	*	*		*	*	
Garcia-Lamberechts et al.	*	*	*	**	*	*	

Outcome		*SCORE*
Was Follow-Up Long Enough for utcomes to Occur	*Adequacy of Follow Up of Cohorts*	*(quality)*
*	*	9 (high)
*	*	9 (high)
*	*	7 (fair)
*	*	9 (high)
*	*	9 (high)
*	*	7 (fair)
*	*	7 (fair)
*		6 (moderate)
*	*	9 (high)
*		6 (moderate)
*	*	9 (high)
*	*	9 (high)
*	*	7 (fair)
*		6 (moderate)
*	*	9 (high)
*		6 (moderate)
*		6 (moderate)
*		6 (moderate)
*	*	7 (fair)
*	*	7 (fair)
*	*	7 (fair)
*	*	9 (high)
*	*	9 (high)
*	*	7 (fair)
*	*	6 (moderate)
*	*	9 (high)
*	*	6 (moderate)
*	*	7 (fair)
*	**	9 (high)
*		7 (fair)
	*	6 (moderate)
	*	7 (fair)
*	*	9 (high)
	*	7 (fair)
*		6 (moderate)
*	*	9 (high)

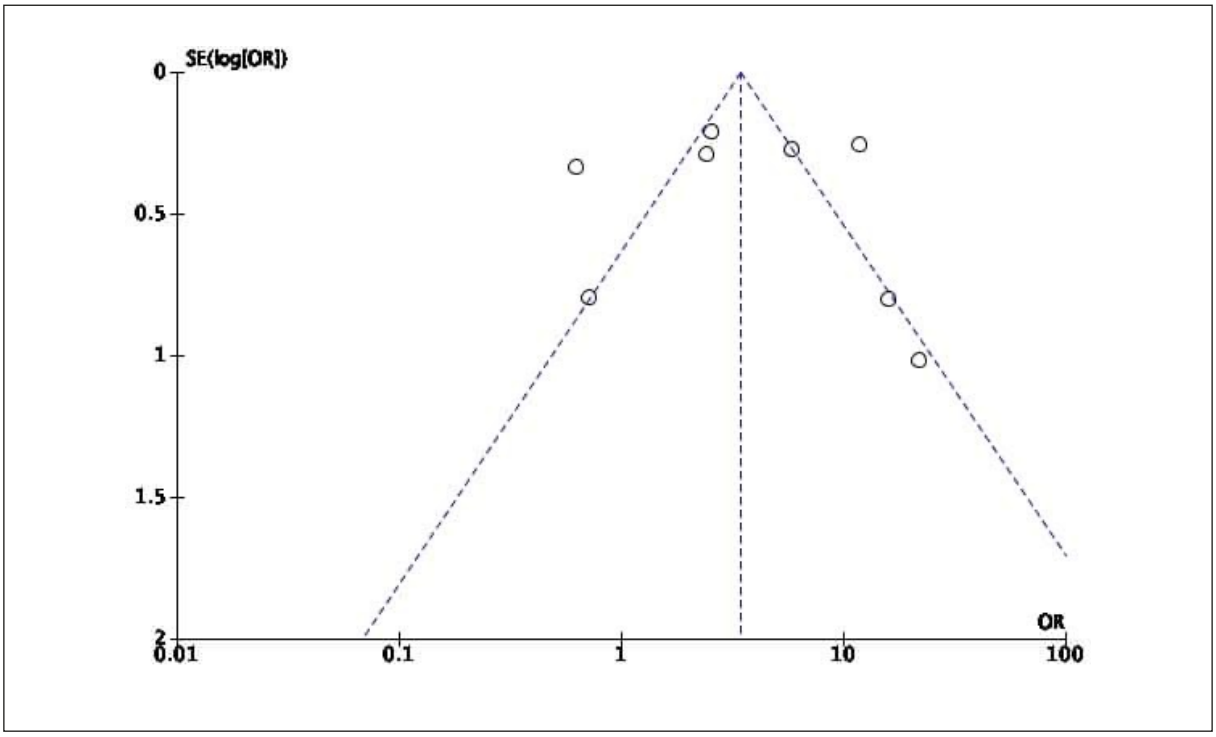

Figure S1 - Funnel plot.

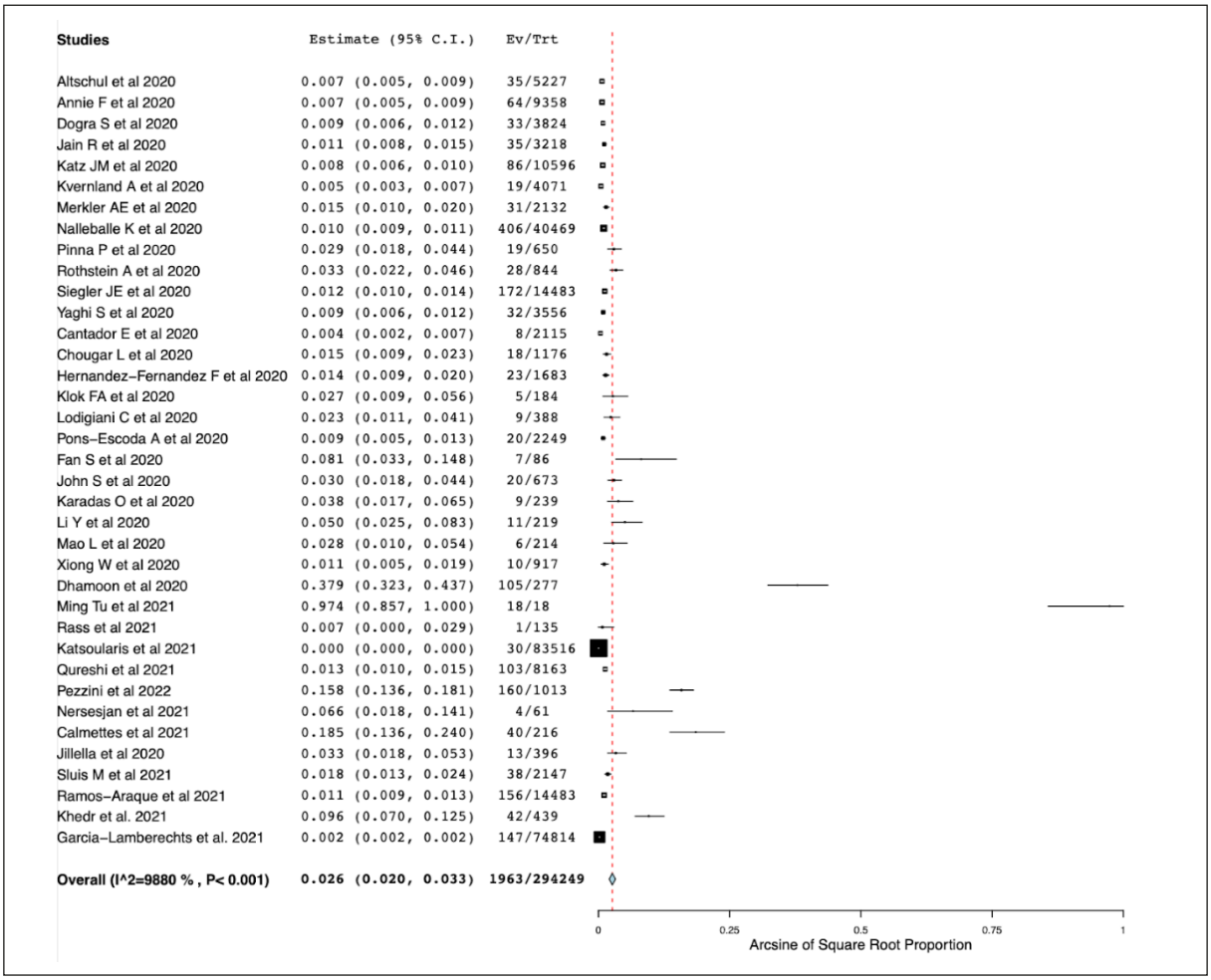

Figure S2 - Forest plot of single-arm analysis of CVD incidence in COVID-19 patients.

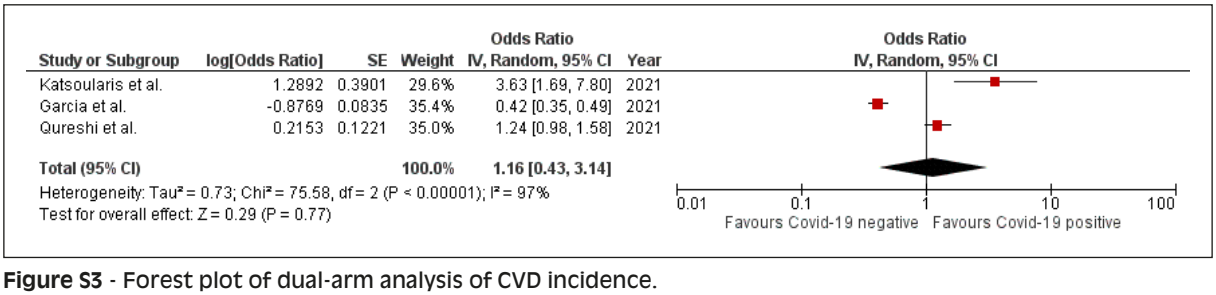

Figure S3 - Forest plot of dual-arm analysis of CVD incidence.

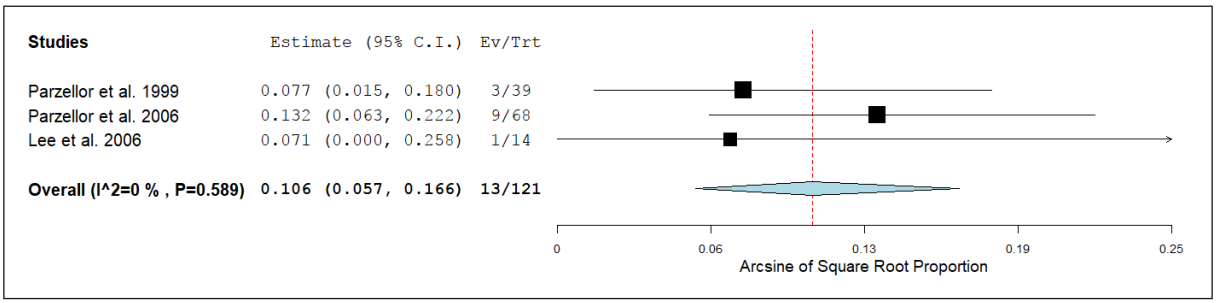

Figure S4 - Diabetes.

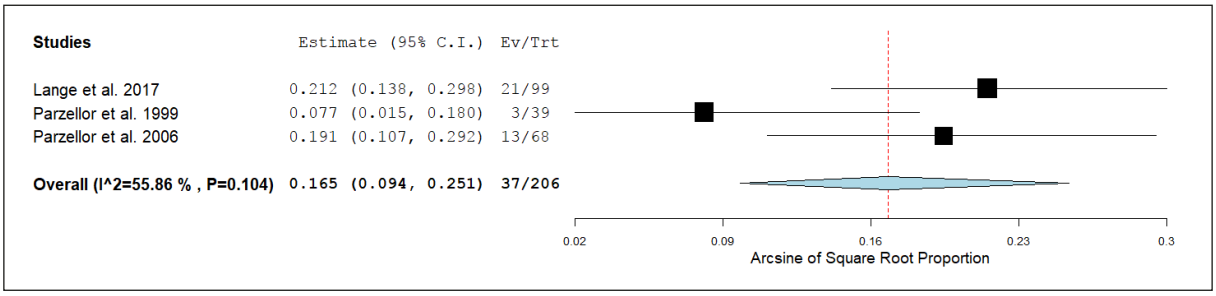

Figure S5 - Hypertension.

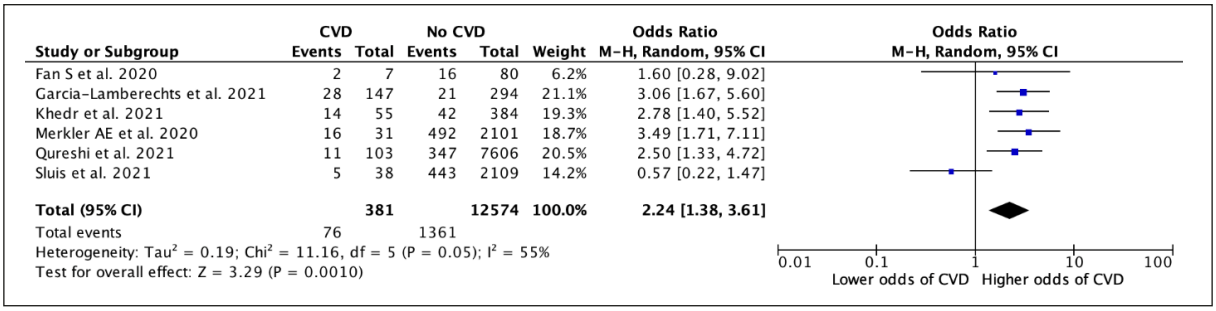

Figure S6 - Coronary artery disease.

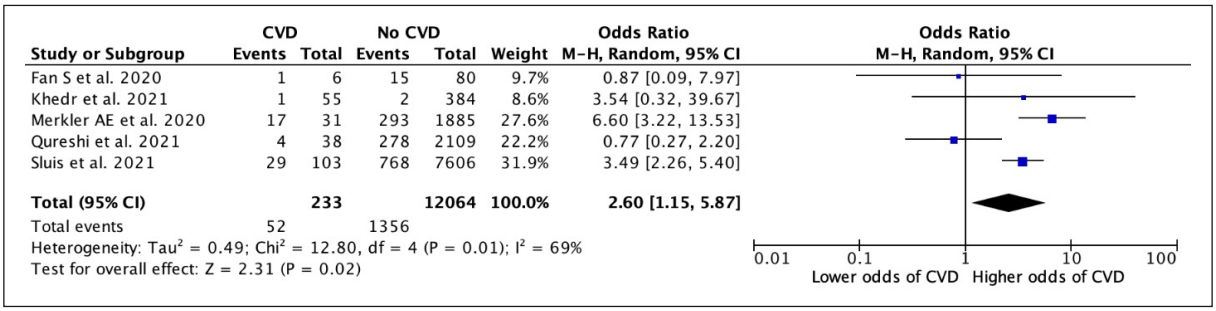

Figure S7 - Atrial fibrillation.

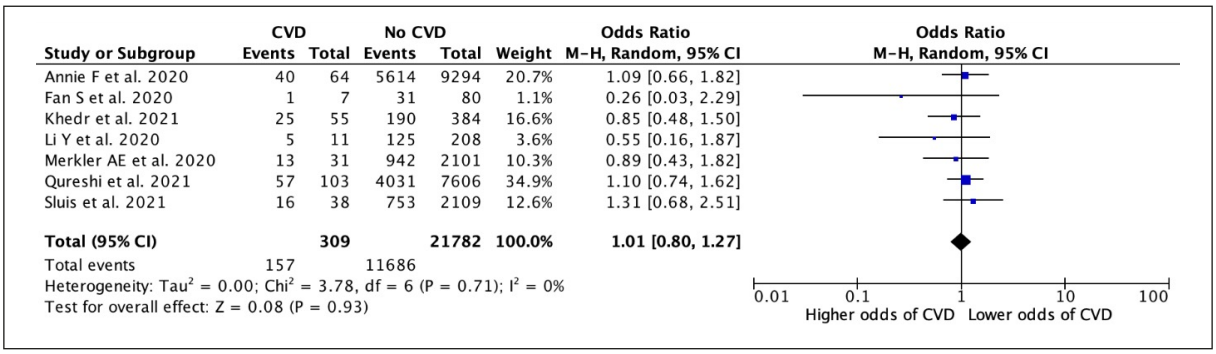

Figure S8 - Female sex.

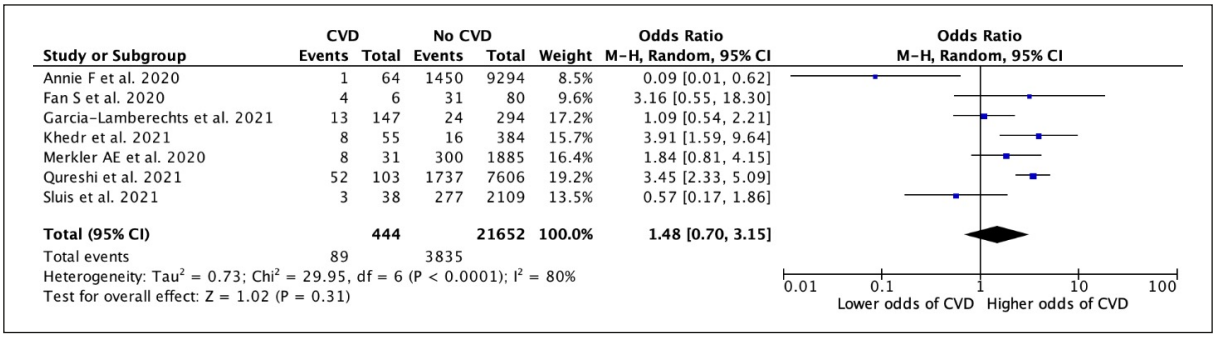

Figure S9 - Kidney injury (acute/chronic).

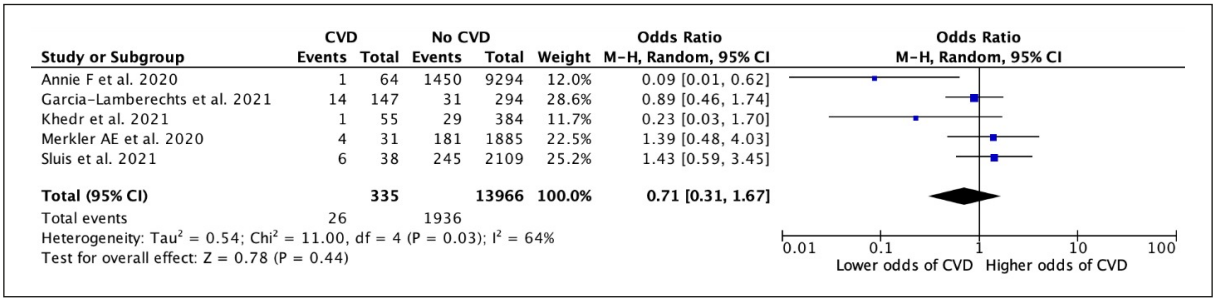

Figure S10 - Chronic obstructive pulmonary disease (COPD).

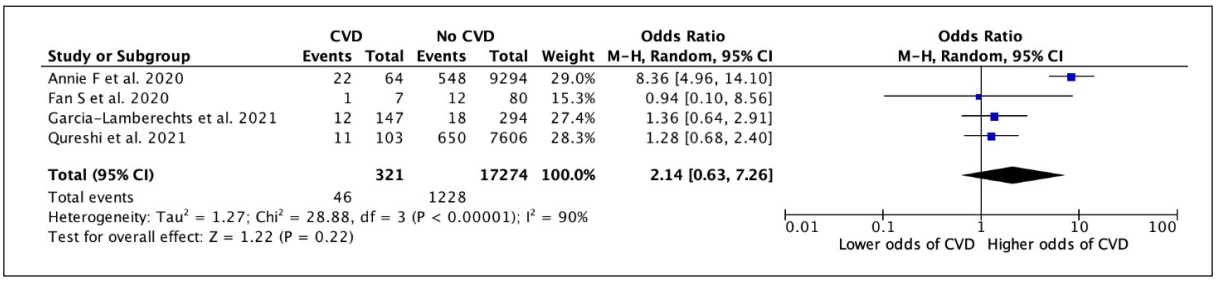

Figure S11 - Smoking.

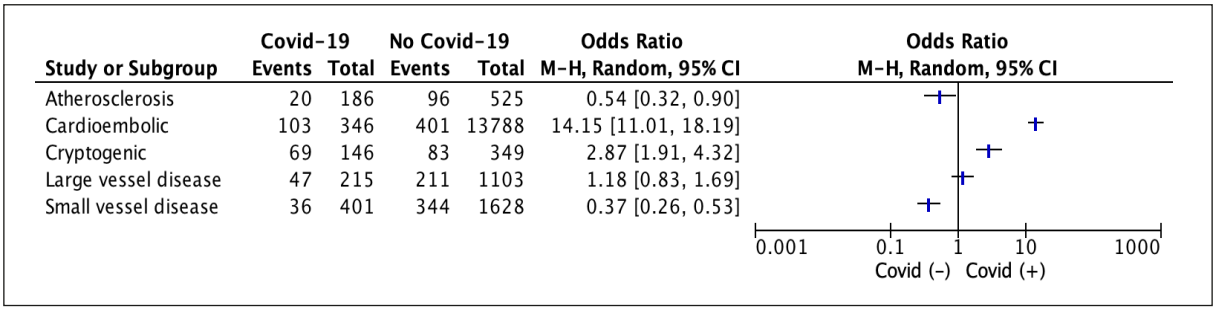

Figure S12 - Forest plot of stroke etiologies among stroke patients with and without COVID-19.